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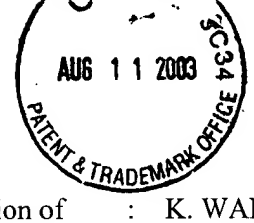

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AF 1626
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Attorney Docket No. P20670

In re application of : K. WANNER et al.

Serial No. : 09/763,617 Group Art Unit: 1626

Filed : June 11, 2001 Examiner: Golam M. Shameem

For : GABA UPTAKE INHIBITORS HAVING A PYRROLIDINE STRUCTURE

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Transmitted herewith is an Appeal Brief Under 37 C.F.R. § 1.192 (in triplicate) in the above-captioned application.

_X_ Small Entity Status of this application under 37 C.F.R. 1.9 and 1.27 has been established by a previously filed statement.
___ A verified statement to establish small entity status under 37 C.F.R. 1.9 and 1.27 is enclosed.
___ A Request for Extension of Time.
___ No Additional Fee.
_X_ Attachment: Exihibit 1 (European Pat. Appln. No. 0 374 801).

The fee has been calculated as shown below:

Claims After Amendment	No. Claims Previously Paid For	Present Extra	Small Entity		Other Than A Small Entity	
			Rate	Fee	Rate	Fee
Total Claims: 31	31*	0	x 9=	$0.00	x 18=	$
Indep. Claims: 3	*3*	0	x 42=	$0.00	x 84=	$
Multiple Dependent Claims Presented			140=	$0.00	+280=	$
Appeal Brief				$160.00		$
			Total:	$160.00	Total:	$

*If less than 20, write 20
**If less than 3, write 3

___ Please charge my Deposit Account No. 19-0089 in the amount of $_____.
_X_ A Check in the amount of $160.00 to cover the appeal brief fee is included.
_X_ The U.S. Patent and Trademark Office is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 19-0089.
_X_ Any additional filing fees required under 37 C.F.R. 1.16.
_X_ Any patent application processing fees under 37 C.F.R. 1.17, including any required extension of time fees in any concurrent or future reply requiring a petition for extension of time for its timely submission (37 CFR 1.136)(a)(3).

Neil F. Greenblum
Reg No. 28,394

Reg No 31,296

P20670.A11

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant :K. WANNER et al.

Group Art Unit : 1626

Serial No. :09/763,617

Examiner: Shameem, Golam M.

Filed :June 11, 2001

For :GABA UPTAKE INHIBITORS HAVING A PYRROLIDINE STRUCTURE

APPEAL BRIEF UNDER 37 C.F.R. § 1.192

Commissioner For Patents
PO Box 1450,
Alexandria, Virginia 23313-1450

Sir:

This Appeal is from the Examiner's Final Rejection of claims 31-61 as set forth in the Final Office Action mailed from the U.S. Patent and Trademark Office on January 10, 2003.

A Notice of Appeal in response to the January 10, 2003 Final Office Action accompanied by a Request for Extension of Time for two months was filed on June 10, 2003.

The requisite fee under 37 C.F.R. 1.17(s) for filing this Appeal Brief as a Small Entity is being paid by check in the amount of $160.00, enclosed herewith.

Inasmuch as this Appeal Brief is being filed within the initial two-month period prescribed by 37 C.F.R. § 1.192, set to expire August 11, 2003 (August 10, 2003 being a Sunday), it is believed that no extension of time is required. However, the Commissioner is authorized to charge any fee necessary for maintaining the pendency of this application,

including any appeal or extension fees that may be necessary, to Deposit Account No. 19-0089.

This Appeal Brief is being submitted in triplicate.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is the assignee BDD Group Holding AG. An executed assignment by which the application was assigned by the previous assignee, BDD Berolina Drug Development AB, to the current assignee was filed with the U.S. Patent and Trademark Office on May 9, 2003. The Notice of Recordation has not yet been received from the Patent and Trademark Office.

II. RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

The status of the claims is as follows:

Claims 31-61 are pending in this application.

Each of claim 31-61 is indicated as rejected in the Final Office Action mailed January 10, 2003.

Each of claims 31-61 is under appeal. These appealed claims 31-61 are reproduced in the Appendix attached hereto.

IV. STATUS OF AMENDMENTS FILED SUBSEQUENT TO FINAL REJECTION

An Amendment under 37 C.F.R. § 1.116 was filed April 22, 2003. According to the Advisory Action mailed from the U.S. Patent and Trademark Office on May 14, 2003, this Amendment has not been entered.

V. SUMMARY OF INVENTION

The present invention is directed to new compounds which show activity as GABA uptake inhibitors, a process for the preparation of these compounds, and pharmaceutical compositions comprising these compounds. The present invention is also directed to a method of treating a disease which can be cured or ameliorated by amplifying GABAergic neurotransmission.

A. Background Information

GABA (gamma-aminobutyric acid) uptake inhibitors are useful in the treatment of various disorders of the central nervous system such as, e.g., epilepsy and Chorea Huntington. As disclosed in Appellants' specification, beginning at page 1, epilepsy is still one of the most common brain disorders, affecting about 50 million patients worldwide. Due to the large variety of seizure forms and a lack of aetiological understanding, therapy approaches are limited to controlling the symptoms, e.g., to the suppression of epileptic fits.

The rudiments of modern therapy go back to the middle of the last century, where bromides were proposed for the treatment of epileptics. In 1912, the anticonvulsive activity

of phenobarbital was discovered. Soon thereafter the first hydantoin derivative was used as an antiepileptic. Like phenobarbital, phenytoin, a hydantoin derivative which was introduced in 1938, is still on the market today. In the late 60's the list of antiepileptics was extended by the benzodiazepines, examples whereof are diazepam and clonazepam.

The mechanisms of action of the individual drugs vary strongly. However, the GABA-mediated inhibition of the excitation transmission is a primary starting point. GABA is an inhibitory neurotransmitter of the central nervous system and is released into the synaptic gap where it modulates the acitivity of other neurons.

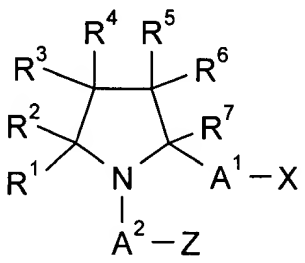
GABA transport proteins are responsible for the uptake of GABA released into the synaptic gap and, thus, for the termination of the neurotransmitter signal. Today, there are four known GABA transport proteins, which are identified as GAT-1, GAT-2, GAT-3 and BGT-1. Compounds which are able to inhibit these proteins will inhibit the uptake of GABA and the undesirable effects associated therewith.

The starting point for the development of GABA uptake inhibitors was the discovery of the inhibiting effect of nipecotic acid and guvacine on the uptake of GABA. However, these compounds can pass the blood-brain barrier only with great difficulty. Meanwhile compounds which pass into the central nervous system more readily and at the same time show affinity towards GABA uptake proteins are available. However, in view of, for example, the existence of at least four different GABA transport proteins that may have to

be inhibited in order to treat the various conditions associated with the undesired uptake of GABA, there is still a need for the development of further compounds which are suitable for effectively (and/or selectively) inhibiting one or more of these different GABA transport proteins.

B. The Invention

The present invention provides a new class of compounds with GABA uptake inhibitory action. In particular, this new class of compounds (including the individual stereoisomers thereof) may be represented by the general formula (I) depicted in independent claim 31, i.e.,



(I)

wherein

R^1 to R^7 are independently selected from H, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, optionally substituted aryl or heteroaryl, OH, halogen, CN, OR^{12}, SR^{12}, COR^{12}, $COOR^{12}$, SOR^{12}, SO_2R^{12}, $NR^{13}R^{14}$, $CONR^{13}R^{14}$, $SO_2NR^{13}R^{14}$, where R^{13} and R^{14} are independently selected from H and C_{1-3} alkyl and R^{12} represents C_{1-6} alkyl ; two of R^1 to R^7, together with the atoms connecting them, each may form a 3- to 6-membered ring system,

which ring system may contain one or more heteroatoms; at least one of the pairs R^1 and R^2; R^3 and R^4; and R^5 and R^6 may be replaced by an optionally substituted alkylidene group or =O; and two of R^1 to R^7 which are positioned at adjacent carbon atoms may each be replaced by a C-C bond;

A^1 is selected from $(-CR^8R^9-)_n$, optionally substituted C_{3-6} cycloalkylene and a combination of these groups, R^8 and R^9 being independently selected from H, C_{1-6} alkyl, halogen, OH, OR^{12} and $NR^{13}R^{14}$ and where for $n \geq 2$, R^8 and R^9 may be different in each group and two groups selected from R^8 and R^9 at adjacent C atoms may be replaced by a C-C bond, and a group -O- or -CO- may be positioned between two adjacent groups CR^8R^9; and wherein one of R^8 and R^9 may be combined with one of R^1 to R^7 to form a 5- to 7-membered ring structure; and n = 1, 2, 3 or 4;

X is selected from COOM and groups which can be converted into COOM under physiological conditions, M being selected from H and pharmaceutically acceptable cations;

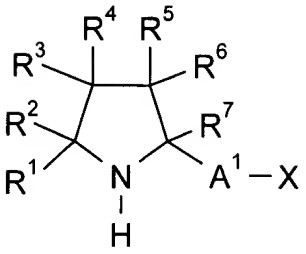
A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H, C_{1-2} alkyl and halogen; where for $m \geq 2$ the groups R^{10} and R^{11} may be different in each group, a group -O- or -S- may be positioned between two adjacent groups $-CR^{10}R^{11}-$, and two groups selected from R^{10} and R^{11} at adjacent C atoms may be replaced by a C-C bond; and wherein one of R^{10} and R^{11} may be combined with one of R^1 to R^9 to form a 5- to 7-membered ring structure; and m is 1, 2, 3, or 4;

Z is selected from Y_3C-O-, Y_2C=CR^{15}- and Y_2C=N-O-, where R^{15} is selected from H, C_{1-3} alkyl or halogen and the groups Y are independently selected from optionally substituted C_{6-12} aryl and optionally substituted C_{2-5} heteroaryl having up to three heteroatoms independently selected from N, O and S, and the groups Y may be linked by a covalent bond or by groups between atoms belonging to different groups Y, said groups selected from -O-, -S-, -NH-, -O-, -CH=CH-, -CH=N-, $-CH_2-$ and $-CH_2CH_2-$.

Preferred representatives of this new class of compounds include the compounds recited in claims 32-56.

The present invention further provides a pharmaceutical composition comprising a compound of general formula (I) as shown above and a pharmaceutically acceptable excipient (claim 59), as well as a method of treating a disease which can be cured or ameliorated by the amplification of GABAeric neurotransmission, which method comprises the administration, to a patient in need thereof, of a compound of the above general formula (I) in an amount sufficient to ameliorate or cure the disease (claim 61).

According to the present invention, the compounds of general formula (I) as shown above may be prepared by the process recited in claim 57, i.e., by a process wherein a compound of formula (II)



(II)

wherein R^1 to R^7, A^1 and X are as recited above is reacted with a compound of formula (III):

$$D - A^2 - Z \quad \text{(III)}$$

wherein A^2 and Z are as recited above and D represents a group which can react with the group N-H of the compound of formula (II) to form HD.

According to dependent claim 58, D comprises halogen.

VI. CONCISE STATEMENT OF ISSUES

The broad issue under consideration is whether claims 31-61 are properly rejected under 35 U.S.C. 103(a) as being unpatentable over BONDINELL in view of SONNEWALD and ALI, in particular, whether a combination of BONDINELL with SONNEWALD and ALI applied in the rejection is sufficient to establish a *prima facie* case of obviousness of the claimed subject matter.

VII. GROUPING OF CLAIMS

An additional issue for consideration is whether at least (a) claims 31-56, (b) claims 59 and 60 and (c) claim 61 are each patentable for separate reasons. Although the rejection in the Examiner's Final Rejection applies to all of claims 31-61, the rejected claims do not

stand or fall together, inasmuch as at least claims 31-56, claims 59 and 60, and claim 61 are separately patentable for reasons described in Section VIII. B., "The Rejected Claims Do Not Stand or Fall Together".

VIII. ARGUMENTS

A. Claims 31-61 Are Not Properly Rejected Under 35 U.S.C. § 103(a) As Being Unpatentable Over BONDINELL In View of SONNEWALD and ALI

The rejection of record misconstrues the documents upon which it is based and, additionally, fails to take into account the accepted wisdom in the field of GABA uptake inhibitors as reflected by a number of documents of record in the instant application.

1. Summary of Rejection of Record

The rejection under 35 U.S.C. § 103(a) is based on the position that U.S. Patent No. 4,514,414 to Bondinell et al. ("BONDINELL") discloses compounds which have GABA uptake inhibitory activity and are position isomers of the compounds of the present invention, i.e., have a group $-A^1X$ in the 3-position of the pyrrolidine ring structure instead of in the 2-position of the pyrrolidine ring structure as in the case of the compounds of the present invention. The rejection alleges that the two other documents on which the rejection is based, i.e., U.S. Patent No. 4,931,450 to Sonnewald ("SONNEWALD") and Ali et al., CAPLUS data base No. 102: 160041 ("ALI"), both teach that in compounds similar in structure to those of BONDINELL, a change from a 3-substitution to a 2-substitution of the central (pyrrolidine) ring does not affect the biological (GABA uptake inhibitory) action. Based on

these alleged facts the Examiner argues:

> One of ordinary skill in the art would consider the instantly claimed position isomers of Bondinell prima facie obvious **because** position isomerism has been used as a tool to obtain new and useful drugs and position isomerism is a fact of close structural similarity. See expate [sic, Ex parte] Engelhardt 208 USPQ 343, In re Mehta 146 USPQ 284. In the instant case not only would one skilled in the art be motivated to choose a position isomer in view of the known teaching in the field. One skill [sic, skilled] in the GABA inhibitor art is deemed to be aware of all pertinent art in the field. Sonnewald and Ali disclosed the ring homologous compounds of Bondinell and taught that substitution at 2-position on the ring carbon and 3-position on the ring carbon would be expected to have similar GABA inhibiting activity. Thus one skill [sic] would be motivated to employ the prima facie structural variation of position isomerism in modifying Bondinell since one would have reasonable expectation that such isomerism would give compounds with similar activity.

Emphasis in original. Office Action mailed August 9, 2002, page 3, paragraph under the heading *Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)*.

The Examiner has subsequently specified his understanding of SONNEWALD and ALI, alleging that

> [i]n Sonnewald, U and Ali et al multiplicity of 2 and 3 substitution compounds have been delineated to have GABA activity (Sonnewald '450, column 3-6; see also homoproline and nipecotic acid compounds structure from CAS registry which is attached herewith for applicant's convenience).

Final Office Action mailed January 10, 2003, page 2, end of third paragraph.

2. The Rejection Fails to Establish a *Prima Facie* Case of Obviousness

"If the Examiner fails to establish a *prima facie* case, the rejection is improper and

will be overturned." In re Rijckaert, 9 F.3d, 1532, 28 U.S.P.Q.2d, 1956 (Fed. Cir. 1993), citing In re Fine, 837 F.2d 1071, 1074,5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The appropriate starting point for a determination of obviousness is stated in Graham v. John Deere Co., 383 U.S. 1, 17, 148 U.S.P.Q. 459, 466 (1966):

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

The test of obviousness *vel non* is statutory and requires a comparison of the claimed subject matter as a whole with the prior art to which the subject matter pertains. In re Brouwer, 77 F.3d, 422, 37 U.S.P.Q.2d 1663 (Fed. Cir. 1996); In re Ochiai, 71 F.3d 1565, 37 U.S.P.Q.2d 1127 (Fed. Cir. 1995). Moreover, the totality of the prior art must be considered, and proceeding contrary to the accepted wisdom in the art is evidence of nonobviousness. In re Hedges, 783 F.2d 1038, 228 U.S.P.Q. 685 (Fed. Cir. 1986), citing W.L. Gore & Assoc., Inc. V. Garlock, Inc., 721 F.2d 1540, 1552, 220 U.S.P.Q. 303, 312 Fed. Cir. 1983), *cert. denied*, and United States v. Adams, 383 U.S. 39, 148 U.S.P.Q. 479 (1966).

In the present application, the Examiner fails to consider the totality of the art. The rejection fails to take into account differences between the claimed invention and the documents of record which are dispositive of the nonobviousness of the present invention. Additionally, as explained below it is evident that the determination of the scope and content

of SONNEWALD and ALI carried out by the Examiner is based on an incorrect interpretation of the disclosure of these documents.

a. SONNEWALD Does Not Teach or Suggest 2-Substituted Compounds

The (mis)understanding underlying the Examiner's arguments in support of the present rejection appears to be that both SONNEWALD and ALI allegedly suggest that compounds having a 3-substituted nitrogen containing ring (i.e., derivatives of nipecotic acid) and corresponding compounds having a 2-substituted ring (i.e., derivatives of "homoproline") have similar GABA uptake inhibitory activity. Based on this understanding, the Examiner essentially argues that one of ordinary skill in the art would have been motivated to modify the 3-substituted compounds of BONDINELL by changing the 3-substitution to a 2-substitution to arrive at compounds of the present invention. However, the Examiner's interpretation of SONNEWALD and ALI is clearly erroneous.

As already pointed out during the personal interview with the Examiner on March 19, 2003, the "homoproline" compounds of SONNEWALD pointed out by the Examiner are derivatives of β-homoproline. β-Homoproline features a **3**-substituted pyrrolidine ring, not a **2**-substituted pyrrolidine ring as apparently assumed by the Examiner. Support for the correct structure of β-homoproline can be found in, e.g., EP 0 374 801 A2 ("EP'801"), a document submitted with the Information Disclosure Statement filed June 4, 2001. A copy of EP'801 is attached hereto as Exhibit 1. One of the inventors mentioned on the face of

EP'801 is Ursula Sonnewald, i.e., the sole inventor mentioned on the face of SONNEWALD.

At page 2, lines 28/29 of EP'801 (filed December 18, 1989) it is expressly stated that "[n]ipecotic acid is piperidine-3-carboxylic acid, guvacine is 1,2,5,6-tetrahydropyridine-3-carboxylic acid and homo-β-proline [i.e., β-homoproline] is pyrrolidine-3-acetic acid". It is noted that the specific compounds mentioned in columns 3-6 of SONNEWALD (filing date October 17, 1988) exclusively are derivatives of either guvacine, nipecotic acid or β-homoproline. Accordingly, all of the specific compounds disclosed in SONNEWALD are derivatives of compounds which have a 3-substituted heterocyclic (nitrogen containing) ring, none of them being a compound having a 2-substituted heterocyclic ring. This is in conformity with the fact that the 3-butenyl compounds of formula (I) as depicted in, e.g., column 1 and claim 1 of SONNEWALD do not have any 2-substituted nitrogen-containing ring as group R^3. In particular, R^3 in said formula (I) is 3-carboxypiperid-1-yl, 3-carboxy-1,2,5,6-tetrahydropyrid-1-yl or 3-carboxymethylpyrrolidin-1-yl, or the corresponding amide, lower alkyl ester or salt group (see, e.g., col. 1, lines 29-32 of SONNEWALD). Thus, contrary to the Examiner's assertion, SONNEWALD does not teach or suggest any 2-substituted compounds, but discloses exclusively 3-substituted compounds.

b. ALI Does Not Teach or Suggest 2-Substituted Compounds

The Examiner's interpretation of the disclosure of ALI is erroneous as well. As noted in Appellants' response filed November 11, 2002, it appears that this document does not

specifically refer to compounds having a 2-substituted pyrrolidine ring, either. For example, the compound of formula I as depicted in ALI is a 3-substituted piperidinecarboxylic acid. While ALI does make reference to "pyrrolidineacetic acids", this document fails to indicate at which position the pyrrolidine ring structure of these compounds is substituted by the carboxymethyl group (2- or 3-position). Moreover, it is to be noted that the authors of ALI include William E. Bondinell and John J. Lafferty, i.e., two of the inventors mentioned on the face of BONDINELL. Therefore, it appears to be safe to assume that the full disclosure of ALI (cited by the Examiner only in the form of an abstract), published in 1985, is similar to that of BONDINELL (filed October 25, 1982), i.e., is directed exclusively to 3-substituted compounds. (An additional reason for this assumption is based on the accepted wisdom in the art as discussed in Section VIII.A.d. below.) Accordingly, ALI does not teach or suggest any 2-substituted compounds, either.

c. A Combination of BONDINELL With SONNEWALD and/or ALI Does Not *Prima Facie* Render Obvious Any 2-Substituted GABA Uptake Inhibitors

Since all three of the documents cited in support of the rejection of present claims 31-61, i.e., BONDINELL, SONNEWALD and ALI, disclose (or can safely be assumed to disclose, respectively) exclusively 3-substituted GABA uptake inhibitors, it is evident that these documents, alone or in any combination thereof, do not render *prima facie* obvious any corresponding 2-substituted compounds. In particular, neither SONNEWALD nor ALI

provide motivation to one of ordinary skill in the art to modify the teaching of BONDINELL by replacing the 3-substitution in the compounds of BONDINELL by a 2-substitution in order to provide new compounds with GABA uptake inhibitory action.

Consequently, the Examiner has not established a *prima facie* case of obviousness of the compounds of the present invention on the basis of BONDINELL in view of SONNEWALD and/or ALI.

d. The Inventors Proceeded Against the Accepted Wisdom In the Art

In the reasons for the rejection of the present claims, the Examiner notes that "one skilled in the GABA inhibitor art is deemed to be aware of all pertinent art in the field". This is an additional reason why a *prima facie* case of obviousness of the present invention has not been established by the Examiner.

As discussed above, all three of the documents applied in the final rejection of the present claims are directed to GABA uptake inhibitors featuring a 3-substituted N-heterocyclic ring (in particular, a 5- or 6-membered ring such as, e.g. pyrrolidine, piperidine, or tetrahydropyridine). These three documents represent but a relatively small fraction of publications which relate to GABA uptake inhibitors having an N-heterocyclic ring the 3-position of which is substituted by a carboxylic group (-COOM), directly or through a linking group such as an alkylene group. Appellants have submitted a number of further examples of such publications - authored by different researchers in different countries and working

for different companies - with the Information Disclosure Statement filed June 4, 2001 (the Examiner has indicated consideration of the Information Disclosure Statement by initialing and signing the Form PTO 1449 submitted therein). In particular, the documents submitted by Appellants (excluding any non-U.S. family members thereof) include:

(1) U.S. Patent No. 5,010,090;

(2) U.S. Patent Nos. 5,053,521 and 5,116,988;

(3) U.S. Patent No. 4,383,999;

(4) U.S. Patent No. 4,931,450;

(5) U.S. Patent No. 5,071,859;

(6) Pavia, Michael R., et al.: Structure-Activity Studies on Benzhydrol-Containing Nipecotic Acid and Guvacine Derivatives as Potent, Orally-Active Inhibitors of GABA Uptake. In: J. Med. Chem. 1992, 35, pp. 4238-4248;

(7) Andersen, Knud Erik, et al.: The Synthesis of Novel GABA Uptake Inhibitors. 1. Elucidation of the Structure-Activity Studies Leading to the Choice of (R)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic Acid (Tiagabine) as an Anticonvulsant Drug Candidate. In: J. Med. Chem. 1993, 36, pp. 1716-1725;

(8) Suzak, Peter D.: Lipophilic GABA uptake inhibitors: Biochemistry, pharmacology and therapeutic potential. In: Drugs of the Future 1993, 18(12), pp.1129-1136;

(9) Murali Dhar, T.G., et al.: Design, Synthesis and Evaluation of Substituted

Triarylnipecotic Acid Derivatives as GABA Uptake Inhibitors: Identification of a Ligand with Moderate Affinity and Selectivity for the Cloned Human GABA Transporter GAT-3. In: J. Med. Chem. 1994, 37, pp. 2334-2342; and

(10) Thomsen, C., et al.: 1-(3-(9H-Carbazol-9-yl)-1-propyl)-4-(2-methoxyphenyl)-4-piperidinol, a novel subtype selective inhibitor of the mouse type II GABA-transporter. In: British Journal of Pharmacology (1997) 120, 983-985.

Like BONDINELL, SONNEWALD and ALI, all of the above documents relate to 3-substituted compounds (and/or 4-substituted compounds in the case of 6-membered rings) which are reported to show GABA uptake inhibitory action. In contrast thereto, there appear to be no documents which were published before the priority date of the present invention (i.e., before September 5, 1998) and show GABA uptake inhibitors which are structurally of the same type as the compounds of the present invention and comprise a 2-substituted N-heterocyclic ring and, in particular, a 2-substituted pyrrolidine ring. This provides ample evidence of the level of ordinary skill in the pertinent art at the time the present invention was made. In particular, what the totality of the submitted documents strongly suggests is that at the time the present invention was made those of skill in the art of GABA uptake inhibitors had accepted that only compounds having a COOM substituent on a ring carbon atom not adjacent to the ring nitrogen atom (i.e., compounds without a COOM substitutent in 2-position) are useful as GABA uptake inhibitors.

Stated differently, contrary to the Examiner's allegation, the totality of the documents of record provides evidence that those of skill in the art did not have an expectation that 2-substituted compounds would have an activity as GABA uptake inhibitors similar to that of the 3-substituted compounds investigated by them.

e. 2-Substituted Compounds Were Available, But Were Not Investigated As GABA Uptake Inhibitors

There are no apparent reasons other than the lack of expectation of success for the lack of interest in 2-substituted compounds by those of skill in the pertinent art. In particular, synthetic obstacles do not appear to have existed. In fact, 2-substituted compounds have been disclosed, albeit for different applications. In this regard, three further documents submitted with Appellants' Information Disclosure Statement may be referred to, i.e., WO 97/45115 A (a family member of U.S. Patent No. 6,191,165 to Ognyanov et al., i.e., the only document cited in the first Office Action mailed December 26, 2001) and GB 2 145 081 A and its family member, U.S. Patent No. 4,610,995. However, neither of these documents relate to GABA uptake inhibitors. Rather, these documents relate to inhibitors of the glycine transport via the Gly-T-1 or Gly-T-2 transporters and to anti-histamines, respectively.

Accordingly, the totality of the numerous documents of record in the present application, including the documents relied on by the Examiner, shows that the present inventors proceeded contrary to the accepted wisdom in the art by employing 2-substituted compounds for the inhibition of GABA uptake rather than 3-(4-) substituted compounds used

by numerous other researchers in this field.

f. Those Skilled in the Art Had Disregarded 2-Substituted Compounds For More Than a Decade

The Examiner argues "that position isomerism has been used as a tool to obtain new and useful drugs and position isomerism is a fact of close structural similarity". However, the Examiner fails to take into account that in the present case there is clear evidence that those of skill in the art apparently did not consider position isomerism to be a useful tool for obtaining new and useful GABA uptake inhibitors. In this regard, it is to be pointed out that at the time the present invention was made, research in the field of GABA uptake inhibitors of the type claimed in the present invention had been going on for much more than a decade (note that the filing date of, for example, BONDINELL is October 25, 1982, more than 15 years before the priority date of the present invention). This would have given those of skill in the art ample time to investigate 2-substituted analogs of any of the known 3-substituted GABA uptake inhibitors. The fact that those skilled in the art apparently did not consider it worthwhile to study 2-substituted compounds with respect to their property as potential GABA uptake inhibitors for many years (otherwise they most likely would have published the results of their studies) and focused exclusively on structural variations of the known 3-substituted compounds without changing the 3-substitution on the heterocyclic ring is yet another strong indication of non-obviousness of the claimed subject matter. Accordingly, a *prima facie* case of obviousness of claims 31-61 has not been established for this additional

reason.

B. The Rejected Claims Do Not Stand or Fall Together

At least claims 31-56, claims 59 and 60, and claim 61 are patentable for separate reasons. It is noted that in light of the documents relied on in the final rejection, compound claims 41-43, 48, 53 and 55 are separately patentable as well, inasmuch as these documents do not teach or suggest any group Z as defined in these claims. However, it also is noted that corresponding groups Z are shown in documents (8) and (9) referred to in Section VIII.A.d. above in combination with GABA uptake inhibitors having a 3-substituted N-heterocyclic ring.

1. Claims 31-56

Compound claim 31, and claims 32-56 depending therefrom, define compounds of general formula (I) as recited in claim 31, all of which have in common that the pyrrolidine ring structure thereof is 2-substituted by a group of formula $-A^1-X$. As discussed above, none of the documents relied on in the final rejection, i.e., BONDINELL, SONNEWALD and ALI, teaches or suggests a compound having a N-heteroaromatic ring with such a group $-A^1-X$ in the 2-position. Therefore, even if it were concluded that any of the remaining composition and method claims 57-61 are not patentable in view of the references relied on in the final rejection for any reason, this reason would not be sufficient to justify a rejection of compound claims 31-56 as *prima facie* obvious over the cited documents.

2. Claims 59 and 60

Composition claim 59 and claim 60 dependent therefrom are directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of general formula (I) as recited in claim 59, with claim 60 reciting a preferred subgenus of the compounds recited in claim 59. As discussed, none of the documents relied on in the final rejection, i.e., BONDINELL, SONNEWALD and ALI, teaches or suggests a compound of general formula (I) as recited in claims 59 and 60, let alone a pharmaceutical composition comprising such a compound. Therefore, even if it were concluded that any of the remaining compound and method claims 31-58 and 61 are not patentable in view of the references relied on in the final rejection for any reason, this reason would not be sufficient to justify a rejection of composition claims 59 and 60 as *prima facie* obvious over the cited documents.

3. Claim 61

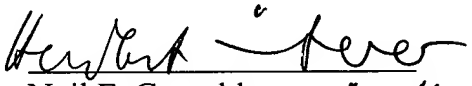
Claim 61 is directed to a method of treating a disease which can be ameliorated or cured by amplification of GABAergenic neurotransmission. According to this method, a compound as recited in independent claim 31 is administered to a patient in need of such treatment in an amount sufficient to ameliorate or cure the disease. As discussed above, none of the documents relied on in the final rejection, i.e., BONDINELL, SONNEWALD and ALI, teaches or suggests a (2-substituted) compound as recited in present claim 31.

Additionally, even if it were assumed, *arguendo*, that such a teaching or suggestion may be found in any of these documents, these documents would still not teach or suggest the use of a corresponding compound for the treatment of a disease which can be ameliorated or cured by amplification of GABAergic neurotransmission. Therefore, even if it were concluded that any of the remaining compound, composition and method claims 31-60 are not patentable in view of the references relied on in the Final Rejection for any reason, this reason would not be sufficient to justify a rejection of method claim 61 as *prima facie* obvious over the cited documents.

IX. CONCLUSION

For the reasons set forth above, it is respectfull submitted that the Examiner has failed to establish a *prima facie* case of obviousness, which is a prerequisite for maintaining a rejection under 35 U.S.C. § 103. The Board is, therefore, respectfully requested to reverse the Final Rejection, and to allow the application to issue in its present form.

Respectfully submitted,
K. WANNER et al.



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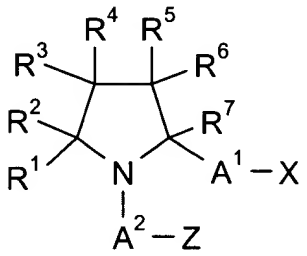
APPENDIX
Copy of Rejected Claims
Rejected Claims 31-61

31. A compound of formula (I)



(I)

wherein

R^1 to R^7 are independently selected from H, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, optionally substituted aryl or heteroaryl, OH, halogen, CN, OR^{12}, SR^{12}, COR^{12}, $COOR^{12}$, SOR^{12}, SO_2R^{12}, $NR^{13}R^{14}$, $CONR^{13}R^{14}$, $SO_2NR^{13}R^{14}$, where R^{13} and R^{14} are independently selected from H and C_{1-3} alkyl and R^{12} represents C_{1-6} alkyl ; two of R^1 to R^7, together with the atoms connecting them, each may form a 3- to 6-membered ring system, which ring system may contain one or more heteroatoms; at least one of the pairs R^1 and R^2; R^3 and R^4; and R^5 and R^6 may be replaced by an optionally substituted alkylidene group or =O; and two of R^1 to R^7 which are positioned at adjacent carbon atoms may each be replaced by a C-C bond;

A^1 is selected from $(-CR^8R^9-)_n$, optionally substituted C_{3-6} cycloalkylene and a combination of these groups, R^8 and R^9 being independently selected from H, C_{1-6} alkyl,

halogen, OH, OR^{12} and $NR^{13}R^{14}$ and where for $n \geq 2$, R^8 and R^9 may be different in each group and two groups selected from R^8 and R^9 at adjacent C atoms may be replaced by a C-C bond, and a group -O- or -CO- may be positioned between two adjacent groups CR^8R^9; and wherein one of R^8 and R^9 may be combined with one of R^1 to R^7 to form a 5- to 7-membered ring structure; and n = 1, 2, 3 or 4;

X is selected from COOM and groups which can be converted into COOM under physiological conditions, M being selected from H and pharmaceutically acceptable cations;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H, C_{1-2} alkyl and halogen; where for $m \geq 2$ the groups R^{10} and R^{11} may be different in each group, a group -O- or -S- may be positioned between two adjacent groups $-CR^{10}R^{11}-$, and two groups selected from R^{10} and R^{11} at adjacent C atoms may be replaced by a C-C bond; and wherein one of R^{10} and R^{11} may be combined with one of R^1 to R^9 to form a 5- to 7-membered ring structure; and m is 1, 2, 3, or 4;

Z is selected from Y_3C-O-, $Y_2C{=}CR^{15}$- and Y_2C=N-O-, where R^{15} is selected from H, C_{1-3} alkyl or halogen and the groups Y are independently selected from optionally substituted C_{6-12} aryl and optionally substituted C heteroaryl having up to three heteroatoms independently selected from N, O and S, and the groups Y may be linked by a covalent bond or by groups between atoms belonging to different groups Y, said groups selected from -O-, -S-, -NH-, -O-, -CH=CH-, -CH=N-, $-CH_2-$ and $-CH_2CH_2-$;

as well as the individual stereoisomers of these compounds.

32. The compound of claim 31, wherein R^7 is hydrogen and R^1 to R^6 are independently selected from hydrogen, optionally substituted C_{1-3} alkyl, halogen, OH, CN, optionally substituted phenyl and optionally substituted heteroaryl having 5 to 10 ring members and one or two heteroatoms selected from O, N and S.

33. The compound of claim 32, wherein R^1 to R^6 are independently selected from hydrogen, C_{1-3} alkyl and phenyl.

34. The compound of claim 33, wherein all of R^1 to R^7 represent hydrogen.

35. The compound of claim 31, wherein A^1 is $(-CR^8R^9-)_n$, R^8 and R^9 are independently selected from H and C_{1-3} alkyl and n has a value of 1, 2 or 3.

36. The compound of claim 35, wherein R^8 and R^9 are each hydrogen and n has a value of 1 or 2.

37. The compound of claim 34, wherein X is COOM, with M = H, Na, K, NH_4, $Ca_{0.5}$ or $Mg_{0.5.}$

38. The compound of claim 37, wherein X is selected from H and Na.

39. The compound of claim 31, wherein R^{10} and R^{11} are independently selected from H and C_{1-2} alkyl and m is 2 or 3.

40. The compound of claim 39, wherein R^{10} and R^{11} are each H and m = 2.

41. The compound of claim 35, wherein Z is Y_3C-O- and the groups Y are phenyl groups optionally substituted with one to two substituents selected from C_{1-3} alkoxy, C_{1-3} alkyl, halogen, OH, NO_2, CN and $NR^{13}R^{14}$.

42. The compound of claim 41, wherein the groups Y are identical and represent phenyl substituted with one C_{1-3} alkoxy group.

43. The compound of claim 42, wherein the phenyl groups are para-substituted with a C_{1-2} alkoxy group.

44. The compound of claim 31, wherein Z is $Y_2C=CR^{15}$-, the groups Y are selected from optionally substituted phenyl and optionally substituted heteroaryl having 5 to 6 ring members and one to two heteroatoms independently selected from O, N and S and R^{15} is selected from H and CH_3.

45. The compound of claim 44, wherein R^{15} is H.

46. The compound of claim 45, wherein the groups Y carry 0, 1 or 2 substituents, the substituents being selected from C_{1-3} alkyl, C_{1-3} alkoxy, halogen, OH, NO_2, CN and $NR^{13}R^{14}$.

47. The compound of claim 44, wherein the groups Y are the same and are selected from phenyl, 4-methoxyphenyl and 3-methyl-2-thienyl.

48. The compound of claim 31, wherein Z is $Y_2C=N-O-$ and the groups Y are selected from optionally substituted phenyl and optionally substituted heteroaryl having 5 to 6 ring members and one to two heteroatoms independently selected from O, N and S.

49. The compound of claim 31, wherein

R^1 to R^7 are independently selected from H, C_{1-3} alkyl and phenyl;

A^1 represents $(-CR^8R^9-)_n$, R^8 and R^9 are independently selected from H and C_{1-3} alkyl, and n = 1 or 2;

X is selected from COOM and groups which can be converted into COOM under physiological conditions, M being selected from H and Na;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H and C_{1-2} alkyl and m is 2 or 3; and

Z is selected from Y_3C-O- and $Y_2C{=}CR^{15}$-, R^{15} is selected from H and methyl and the groups Y are identical and selected from optionally substituted C_{6-12} aryl and optionally substituted C_{2-5} heteroaryl having up to three heteroatoms independently selected from N, O and S.

50. The compound of claim 49, wherein R^1 to R^7 are independently selected from H and methyl.

51. The compound of claim 50, wherein R^8 and R^9 are independently selected from H and methyl, and n = 1.

52. The compound of claim 49, wherein R^{10} and R^{11} are independently selected

from H and C_{1-2} alkyl and m is 2 .

53. The compound of claim 52, wherein Z is Y_3C-O- and the groups Y are identical and represent phenyl substituted with one C_{1-3} alkoxy group.

54. The compound of claim 49, wherein Z is Y_2C=CH- and the groups Y are identical and selected from phenyl, 4-methoxyphenyl and 3-methyl-2-thienyl.

55. The compound of claim 49, wherein

R^1 to R^7 are each H;

A^1 represents $(-CR^8R^9-)_n$, R^8 and R^9 are independently selected from H and methyl, and n = 1 or 2;

X is COOM and M is selected from H and Na;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H and methyl and m is 2; and

Z is Y_3C-O- and the groups Y are identical and selected from phenyl groups para-substituted with a C_{1-2} alkoxy group.

56. The compound of claim 49, wherein

R^1 to R^7 are each H;

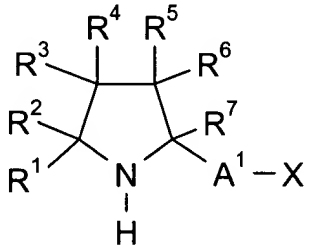
A^1 represents $(-CR^8R^9-)_n$, R^8 and R^9 are independently selected from H and methyl, and n = 1 or 2;

X is COOM and M is selected from H and Na;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H and methyl and m is 2; and

Z is Y_2C=CH- and the groups Y are identical and selected from phenyl, 4-methoxyphenyl and 3-methyl-2-thienyl.

57. A process for the preparation of a compound of formula (I) of claim 31, wherein a compound of formula (II)



(II)

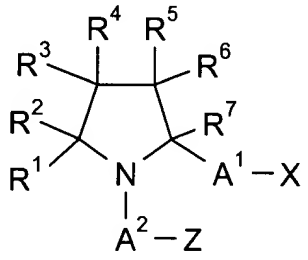
wherein R^1 to R^7, A^1 and X are as defined in claim 31 is reacted with a compound of formula (III):

$$D - A^2 - Z \quad \text{(III)}$$

wherein A^2 and Z are defined as in claim 31 and D represents a group which can react with the group N-H of the compound of formula (II) to form HD.

58. The process of claim 57, wherein D is halogen.

59. A pharmaceutical composition comprising at least one of a pharmaceutically acceptable carrier and a pharmaceutically acceptable excipient and at least one compound of formula (I):



(I)

wherein

R^1 to R^7 are independently selected from H, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, optionally substituted aryl or heteroaryl, OH, halogen, CN, OR^{12}, SR^{12}, COR^{12}, $COOR^{12}$, SOR^{12}, SO_2R^{12}, $NR^{13}R^{14}$, $CONR^{13}R^{14}$, $SO_2NR^{13}R^{14}$, where R^{13} and R^{14} are independently selected from H and C_{1-3} alkyl and R^{12} represents C_{1-6} alkyl ; two of R^1 to R^7, together with the atoms connecting them, each may form a 3- to 6-membered ring system, which ring system may contain one or more heteroatoms; at least one of the pairs R^1 and R^2; R^3 and R^4; and R^5 and R^6 may be replaced by an optionally substituted alkylidene group or

=O; and two of R^1 to R^7 which are positioned at adjacent carbon atoms may each be replaced by a C-C bond;

A^1 is selected from $(-CR^8R^9-)_n$, optionally substituted C_{3-6} cycloalkylene and a combination of these groups, R^8 and R^9 being independently selected from H, C_{1-6} alkyl, halogen, OH, OR^{12} and $NR^{13}R^{14}$ and where for $n \geq 2$, R^8 and R^9 may be different in each group and two groups selected from R^8 and R^9 at adjacent C atoms may be replaced by a C-C bond, and a group -O- or -CO- may be positioned between two adjacent groups CR^8R^9; and wherein one of R^8 and R^9 may be combined with one of R^1 to R^7 to form a 5- to 7-membered ring structure; and n = 1, 2, 3 or 4;

X is selected from COOM and groups which can be converted into COOM under physiological conditions, M being selected from H and pharmaceutically acceptable cations;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H, C_{1-2} alkyl and halogen; where for $m \geq 2$ the groups R^{10} and R^{11} may be different in each group, a group -O- or -S- may be positioned between two adjacent groups $-CR^{10}R^{11}-$, and two groups selected from R^{10} and R^{11} at adjacent C atoms may be replaced by a C-C bond; and wherein one of R^{10} and R^{11} may be combined with one of R^1 to R^9 to form a 5- to 7-membered ring structure; and m is 1, 2, 3, or 4;

Z is selected from Y_3C-O-, $Y_2C{=}CR^{15}$- and $Y_2C{=}N$-O-, where R^{15} is selected from H, C_{1-3} alkyl or halogen and the groups Y are independently selected from optionally substituted

C_{6-12} aryl and optionally substituted C_{2-5} heteroaryl having up to three heteroatoms independently selected from N, O and S, and the groups Y may be linked by a covalent bond or by groups between atoms belonging to different groups Y, said groups selected from -O-, -S-, -NH-, -O-, -CH=CH-, -CH=N-, $-CH_2-$ and $-CH_2CH_2-$.

60. The pharmaceutical composition of claim 59, wherein

R^1 to R^7 are independently selected from H, C_{1-3} alkyl and phenyl;

A^1 represents $(-CR^8R^9-)_n$, R^8 and R^9 are independently selected from H and C_{1-3} alkyl, and n = 1 or 2;

X is selected from COOM and groups which can be converted into COOM under physiological conditions, M being selected from H and Na;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H and C_{1-2} alkyl and m is 2 or 3; and

Z is selected from Y_3C-O- and $Y_2C=CR^{15}$-, R^{15} is selected from H and methyl and the groups Y are identical and selected from optionally substituted C_{6-12} aryl and optionally substituted C_{2-5} heteroaryl having up to three heteroatoms independently selected from N, O and S.

61. A method of treating a disease which can be one of ameliorated and cured by

amplification of GABAergenic neurotransmission, the method comprising administering to a patient in need of such treatment a compound of claim 31 in an amount sufficient to ameliorate or cure the disease.

P20670.A11

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant :K. WANNER et al.

Group Art Unit : 1626

Serial No. :09/763,617

Examiner: Shameem, Golam M.

Filed :June 11, 2001

For :GABA UPTAKE INHIBITORS HAVING A PYRROLIDINE STRUCTURE

APPEAL BRIEF UNDER 37 C.F.R. § 1.192

Commissioner For Patents
PO Box 1450,
Alexandria, Virginia 23313-1450

Sir:

This Appeal is from the Examiner's Final Rejection of claims 31-61 as set forth in the Final Office Action mailed from the U.S. Patent and Trademark Office on January 10, 2003.

A Notice of Appeal in response to the January 10, 2003 Final Office Action accompanied by a Request for Extension of Time for two months was filed on June 10, 2003.

The requisite fee under 37 C.F.R. 1.17(s) for filing this Appeal Brief as a Small Entity is being paid by check in the amount of $160.00, enclosed herewith.

Inasmuch as this Appeal Brief is being filed within the initial two-month period prescribed by 37 C.F.R. § 1.192, set to expire August 11, 2003 (August 10, 2003 being a Sunday), it is believed that no extension of time is required. However, the Commissioner is authorized to charge any fee necessary for maintaining the pendency of this application,

including any appeal or extension fees that may be necessary, to Deposit Account No. 19-0089.

This Appeal Brief is being submitted in triplicate.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is the assignee BDD Group Holding AG. An executed assignment by which the application was assigned by the previous assignee, BDD Berolina Drug Development AB, to the current assignee was filed with the U.S. Patent and Trademark Office on May 9, 2003. The Notice of Recordation has not yet been received from the Patent and Trademark Office.

II. RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

The status of the claims is as follows:

Claims 31-61 are pending in this application.

Each of claim 31-61 is indicated as rejected in the Final Office Action mailed January 10, 2003.

Each of claims 31-61 is under appeal. These appealed claims 31-61 are reproduced in the Appendix attached hereto.

IV. STATUS OF AMENDMENTS FILED SUBSEQUENT TO FINAL REJECTION

An Amendment under 37 C.F.R. § 1.116 was filed April 22, 2003. According to the Advisory Action mailed from the U.S. Patent and Trademark Office on May 14, 2003, this Amendment has not been entered.

V. SUMMARY OF INVENTION

The present invention is directed to new compounds which show activity as GABA uptake inhibitors, a process for the preparation of these compounds, and pharmaceutical compositions comprising these compounds. The present invention is also directed to a method of treating a disease which can be cured or ameliorated by amplifying GABAergic neurotransmission.

A. Background Information

GABA (gamma-aminobutyric acid) uptake inhibitors are useful in the treatment of various disorders of the central nervous system such as, e.g., epilepsy and Chorea Huntington. As disclosed in Appellants' specification, beginning at page 1, epilepsy is still one of the most common brain disorders, affecting about 50 million patients worldwide. Due to the large variety of seizure forms and a lack of aetiological understanding, therapy approaches are limited to controlling the symptoms, e.g., to the suppression of epileptic fits.

The rudiments of modern therapy go back to the middle of the last century, where bromides were proposed for the treatment of epileptics. In 1912, the anticonvulsive activity

of phenobarbital was discovered. Soon thereafter the first hydantoin derivative was used as an antiepileptic. Like phenobarbital, phenytoin, a hydantoin derivative which was introduced in 1938, is still on the market today. In the late 60's the list of antiepileptics was extended by the benzodiazepines, examples whereof are diazepam and clonazepam.

The mechanisms of action of the individual drugs vary strongly. However, the GABA-mediated inhibition of the excitation transmission is a primary starting point. GABA is an inhibitory neurotransmitter of the central nervous system and is released into the synaptic gap where it modulates the acitivity of other neurons.

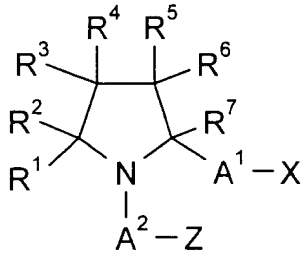
GABA transport proteins are responsible for the uptake of GABA released into the synaptic gap and, thus, for the termination of the neurotransmitter signal. Today, there are four known GABA transport proteins, which are identified as GAT-1, GAT-2, GAT-3 and BGT-1. Compounds which are able to inhibit these proteins will inhibit the uptake of GABA and the undesirable effects associated therewith.

The starting point for the development of GABA uptake inhibitors was the discovery of the inhibiting effect of nipecotic acid and guvacine on the uptake of GABA. However, these compounds can pass the blood-brain barrier only with great difficulty. Meanwhile compounds which pass into the central nervous system more readily and at the same time show affinity towards GABA uptake proteins are available. However, in view of, for example, the existence of at least four different GABA transport proteins that may have to

be inhibited in order to treat the various conditions associated with the undesired uptake of GABA, there is still a need for the development of further compounds which are suitable for effectively (and/or selectively) inhibiting one or more of these different GABA transport proteins.

B. The Invention

The present invention provides a new class of compounds with GABA uptake inhibitory action. In particular, this new class of compounds (including the individual stereoisomers thereof) may be represented by the general formula (I) depicted in independent claim 31, i.e.,



(I)

wherein

R^1 to R^7 are independently selected from H, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, optionally substituted aryl or heteroaryl, OH, halogen, CN, OR^{12}, SR^{12}, COR^{12}, $COOR^{12}$, SOR^{12}, SO_2R^{12}, $NR^{13}R^{14}$, $CONR^{13}R^{14}$, $SO_2NR^{13}R^{14}$, where R^{13} and R^{14} are independently selected from H and C_{1-3} alkyl and R^{12} represents C_{1-6} alkyl ; two of R^1 to R^7, together with the atoms connecting them, each may form a 3- to 6-membered ring system,

which ring system may contain one or more heteroatoms; at least one of the pairs R^1 and R^2; R^3 and R^4; and R^5 and R^6 may be replaced by an optionally substituted alkylidene group or =O; and two of R^1 to R^7 which are positioned at adjacent carbon atoms may each be replaced by a C-C bond;

A^1 is selected from $(-CR^8R^9-)_n$, optionally substituted C_{3-6} cycloalkylene and a combination of these groups, R^8 and R^9 being independently selected from H, C_{1-6} alkyl, halogen, OH, OR^{12} and $NR^{13}R^{14}$ and where for $n \geq 2$, R^8 and R^9 may be different in each group and two groups selected from R^8 and R^9 at adjacent C atoms may be replaced by a C-C bond, and a group -O- or -CO- may be positioned between two adjacent groups CR^8R^9; and wherein one of R^8 and R^9 may be combined with one of R^1 to R^7 to form a 5- to 7-membered ring structure; and n = 1, 2, 3 or 4;

X is selected from COOM and groups which can be converted into COOM under physiological conditions, M being selected from H and pharmaceutically acceptable cations;

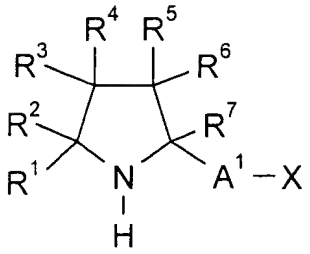
A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H, C_{1-2} alkyl and halogen; where for $m \geq 2$ the groups R^{10} and R^{11} may be different in each group, a group -O- or -S- may be positioned between two adjacent groups $-CR^{10}R^{11}-$, and two groups selected from R^{10} and R^{11} at adjacent C atoms may be replaced by a C-C bond; and wherein one of R^{10} and R^{11} may be combined with one of R^1 to R^9 to form a 5- to 7-membered ring structure; and m is 1, 2, 3, or 4;

Z is selected from Y_3C-O-, Y_2C=CR^{15}- and Y_2C=N-O-, where R^{15} is selected from H, C_{1-3} alkyl or halogen and the groups Y are independently selected from optionally substituted C_{6-12} aryl and optionally substituted C_{2-5} heteroaryl having up to three heteroatoms independently selected from N, O and S, and the groups Y may be linked by a covalent bond or by groups between atoms belonging to different groups Y, said groups selected from -O-, -S-, -NH-, -O-, -CH=CH-, -CH=N-, $-CH_2-$ and $-CH_2CH_2-$.

Preferred representatives of this new class of compounds include the compounds recited in claims 32-56.

The present invention further provides a pharmaceutical composition comprising a compound of general formula (I) as shown above and a pharmaceutically acceptable excipient (claim 59), as well as a method of treating a disease which can be cured or ameliorated by the amplification of GABAeric neurotransmission, which method comprises the administration, to a patient in need thereof, of a compound of the above general formula (I) in an amount sufficient to ameliorate or cure the disease (claim 61).

According to the present invention, the compounds of general formula (I) as shown above may be prepared by the process recited in claim 57, i.e., by a process wherein a compound of formula (II)



(II)

wherein R^1 to R^7, A^1 and X are as recited above is reacted with a compound of formula (III):

$$D - A^2 - Z \qquad \text{(III)}$$

wherein A^2 and Z are as recited above and D represents a group which can react with the group N-H of the compound of formula (II) to form HD.

According to dependent claim 58, D comprises halogen.

VI. CONCISE STATEMENT OF ISSUES

The broad issue under consideration is whether claims 31-61 are properly rejected under 35 U.S.C. 103(a) as being unpatentable over BONDINELL in view of SONNEWALD and ALI, in particular, whether a combination of BONDINELL with SONNEWALD and ALI applied in the rejection is sufficient to establish a *prima facie* case of obviousness of the claimed subject matter.

VII. GROUPING OF CLAIMS

An additional issue for consideration is whether at least (a) claims 31-56, (b) claims 59 and 60 and (c) claim 61 are each patentable for separate reasons. Although the rejection in the Examiner's Final Rejection applies to all of claims 31-61, the rejected claims do not

stand or fall together, inasmuch as at least claims 31-56, claims 59 and 60, and claim 61 are separately patentable for reasons described in Section VIII. B., "The Rejected Claims Do Not Stand or Fall Together".

VIII. ARGUMENTS

A. Claims 31-61 Are Not Properly Rejected Under 35 U.S.C. § 103(a) As Being Unpatentable Over BONDINELL In View of SONNEWALD and ALI

The rejection of record misconstrues the documents upon which it is based and, additionally, fails to take into account the accepted wisdom in the field of GABA uptake inhibitors as reflected by a number of documents of record in the instant application.

1. Summary of Rejection of Record

The rejection under 35 U.S.C. § 103(a) is based on the position that U.S. Patent No. 4,514,414 to Bondinell et al. ("BONDINELL") discloses compounds which have GABA uptake inhibitory activity and are position isomers of the compounds of the present invention, i.e., have a group $-A^1X$ in the 3-position of the pyrrolidine ring structure instead of in the 2-position of the pyrrolidine ring structure as in the case of the compounds of the present invention. The rejection alleges that the two other documents on which the rejection is based, i.e., U.S. Patent No. 4,931,450 to Sonnewald ("SONNEWALD") and Ali et al., CAPLUS data base No. 102: 160041 ("ALI"), both teach that in compounds similar in structure to those of BONDINELL, a change from a 3-substitution to a 2-substitution of the central (pyrrolidine) ring does not affect the biological (GABA uptake inhibitory) action. Based on

these alleged facts the Examiner argues:

> One of ordinary skill in the art would consider the instantly claimed position isomers of Bondinell prima facie obvious **because** position isomerism has been used as a tool to obtain new and useful drugs and position isomerism is a fact of close structural similarity. See expate [sic, Ex parte] Engelhardt 208 USPQ 343, In re Mehta 146 USPQ 284. In the instant case not only would one skilled in the art be motivated to choose a position isomer in view of the known teaching in the field. One skill [sic, skilled] in the GABA inhibitor art is deemed to be aware of all pertinent art in the field. Sonnewald and Ali disclosed the ring homologous compounds of Bondinell and taught that substitution at 2-position on the ring carbon and 3-position on the ring carbon would be expected to have similar GABA inhibiting activity. Thus one skill [sic] would be motivated to employ the prima facie structural variation of position isomerism in modifying Bondinell since one would have reasonable expectation that such isomerism would give compounds with similar activity.

Emphasis in original. Office Action mailed August 9, 2002, page 3, paragraph under the heading *Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)*.

The Examiner has subsequently specified his understanding of SONNEWALD and ALI, alleging that

> [i]n Sonnewald, U and Ali et al multiplicity of 2 and 3 substitution compounds have been delineated to have GABA activity (Sonnewald '450, column 3-6; see also homoproline and nipecotic acid compounds structure from CAS registry which is attached herewith for applicant's convenience).

Final Office Action mailed January 10, 2003, page 2, end of third paragraph.

2. The Rejection Fails to Establish a *Prima Facie* Case of Obviousness

"If the Examiner fails to establish a *prima facie* case, the rejection is improper and

will be overturned." In re Rijckaert, 9 F.3d, 1532, 28 U.S.P.Q.2d, 1956 (Fed. Cir. 1993), citing In re Fine, 837 F.2d 1071, 1074,5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The appropriate starting point for a determination of obviousness is stated in Graham v. John Deere Co., 383 U.S. 1, 17, 148 U.S.P.Q. 459, 466 (1966):

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

The test of obviousness *vel non* is statutory and requires a comparison of the claimed subject matter as a whole with the prior art to which the subject matter pertains. In re Brouwer, 77 F.3d, 422, 37 U.S.P.Q.2d 1663 (Fed. Cir. 1996); In re Ochiai, 71 F.3d 1565, 37 U.S.P.Q.2d 1127 (Fed. Cir. 1995). Moreover, the totality of the prior art must be considered, and proceeding contrary to the accepted wisdom in the art is evidence of nonobviousness. In re Hedges, 783 F.2d 1038, 228 U.S.P.Q. 685 (Fed. Cir. 1986), citing W.L. Gore & Assoc., Inc. V. Garlock, Inc., 721 F.2d 1540, 1552, 220 U.S.P.Q. 303, 312 Fed. Cir. 1983), *cert. denied*, and United States v. Adams, 383 U.S. 39, 148 U.S.P.Q. 479 (1966).

In the present application, the Examiner fails to consider the totality of the art. The rejection fails to take into account differences between the claimed invention and the documents of record which are dispositive of the nonobviousness of the present invention. Additionally, as explained below it is evident that the determination of the scope and content

of SONNEWALD and ALI carried out by the Examiner is based on an incorrect interpretation of the disclosure of these documents.

a. SONNEWALD Does Not Teach or Suggest 2-Substituted Compounds

The (mis)understanding underlying the Examiner's arguments in support of the present rejection appears to be that both SONNEWALD and ALI allegedly suggest that compounds having a 3-substituted nitrogen containing ring (i.e., derivatives of nipecotic acid) and corresponding compounds having a 2-substituted ring (i.e., derivatives of "homoproline") have similar GABA uptake inhibitory activity. Based on this understanding, the Examiner essentially argues that one of ordinary skill in the art would have been motivated to modify the 3-substituted compounds of BONDINELL by changing the 3-substitution to a 2-substitution to arrive at compounds of the present invention. However, the Examiner's interpretation of SONNEWALD and ALI is clearly erroneous.

As already pointed out during the personal interview with the Examiner on March 19, 2003, the "homoproline" compounds of SONNEWALD pointed out by the Examiner are derivatives of β-homoproline. β-Homoproline features a **3**-substituted pyrrolidine ring, not a **2**-substituted pyrrolidine ring as apparently assumed by the Examiner. Support for the correct structure of β-homoproline can be found in, e.g., EP 0 374 801 A2 ("EP'801"), a document submitted with the Information Disclosure Statement filed June 4, 2001. A copy of EP'801 is attached hereto as Exhibit 1. One of the inventors mentioned on the face of

EP'801 is Ursula Sonnewald, i.e., the sole inventor mentioned on the face of SONNEWALD.

At page 2, lines 28/29 of EP'801 (filed December 18, 1989) it is expressly stated that "[n]ipecotic acid is piperidine-3-carboxylic acid, guvacine is 1,2,5,6-tetrahydropyridine-3-carboxylic acid and homo-β-proline [i.e., β-homoproline] is pyrrolidine-3-acetic acid". It is noted that the specific compounds mentioned in columns 3-6 of SONNEWALD (filing date October 17, 1988) exclusively are derivatives of either guvacine, nipecotic acid or β-homoproline. Accordingly, all of the specific compounds disclosed in SONNEWALD are derivatives of compounds which have a 3-substituted heterocyclic (nitrogen containing) ring, none of them being a compound having a 2-substituted heterocyclic ring. This is in conformity with the fact that the 3-butenyl compounds of formula (I) as depicted in, e.g., column 1 and claim 1 of SONNEWALD do not have any 2-substituted nitrogen-containing ring as group R^3. In particular, R^3 in said formula (I) is 3-carboxypiperid-1-yl, 3-carboxy-1,2,5,6-tetrahydropyrid-1-yl or 3-carboxymethylpyrrolidin-1-yl, or the corresponding amide, lower alkyl ester or salt group (see, e.g., col. 1, lines 29-32 of SONNEWALD). Thus, contrary to the Examiner's assertion, SONNEWALD does not teach or suggest any 2-substituted compounds, but discloses exclusively 3-substituted compounds.

b. ALI Does Not Teach or Suggest 2-Substituted Compounds

The Examiner's interpretation of the disclosure of ALI is erroneous as well. As noted in Appellants' response filed November 11, 2002, it appears that this document does not

specifically refer to compounds having a 2-substituted pyrrolidine ring, either. For example, the compound of formula I as depicted in ALI is a 3-substituted piperidinecarboxylic acid. While ALI does make reference to "pyrrolidineacetic acids", this document fails to indicate at which position the pyrrolidine ring structure of these compounds is substituted by the carboxymethyl group (2- or 3-position). Moreover, it is to be noted that the authors of ALI include William E. Bondinell and John J. Lafferty, i.e., two of the inventors mentioned on the face of BONDINELL. Therefore, it appears to be safe to assume that the full disclosure of ALI (cited by the Examiner only in the form of an abstract), published in 1985, is similar to that of BONDINELL (filed October 25, 1982), i.e., is directed exclusively to 3-substituted compounds. (An additional reason for this assumption is based on the accepted wisdom in the art as discussed in Section VIII.A.d. below.) Accordingly, ALI does not teach or suggest any 2-substituted compounds, either.

c. A Combination of BONDINELL With SONNEWALD and/or ALI Does Not *Prima Facie* Render Obvious Any 2-Substituted GABA Uptake Inhibitors

Since all three of the documents cited in support of the rejection of present claims 31-61, i.e., BONDINELL, SONNEWALD and ALI, disclose (or can safely be assumed to disclose, respectively) exclusively 3-substituted GABA uptake inhibitors, it is evident that these documents, alone or in any combination thereof, do not render *prima facie* obvious any corresponding 2-substituted compounds. In particular, neither SONNEWALD nor ALI

provide motivation to one of ordinary skill in the art to modify the teaching of BONDINELL by replacing the 3-substitution in the compounds of BONDINELL by a 2-substitution in order to provide new compounds with GABA uptake inhibitory action.

Consequently, the Examiner has not established a *prima facie* case of obviousness of the compounds of the present invention on the basis of BONDINELL in view of SONNEWALD and/or ALI.

d. The Inventors Proceeded Against the Accepted Wisdom In the Art

In the reasons for the rejection of the present claims, the Examiner notes that "one skilled in the GABA inhibitor art is deemed to be aware of all pertinent art in the field". This is an additional reason why a *prima facie* case of obviousness of the present invention has not been established by the Examiner.

As discussed above, all three of the documents applied in the final rejection of the present claims are directed to GABA uptake inhibitors featuring a 3-substituted N-heterocyclic ring (in particular, a 5- or 6-membered ring such as, e.g. pyrrolidine, piperidine, or tetrahydropyridine). These three documents represent but a relatively small fraction of publications which relate to GABA uptake inhibitors having an N-heterocyclic ring the 3-position of which is substituted by a carboxylic group (-COOM), directly or through a linking group such as an alkylene group. Appellants have submitted a number of further examples of such publications - authored by different researchers in different countries and working

for different companies - with the Information Disclosure Statement filed June 4, 2001 (the Examiner has indicated consideration of the Information Disclosure Statement by initialing and signing the Form PTO 1449 submitted therein). In particular, the documents submitted by Appellants (excluding any non-U.S. family members thereof) include:

(1) U.S. Patent No. 5,010,090;

(2) U.S. Patent Nos. 5,053,521 and 5,116,988;

(3) U.S. Patent No. 4,383,999;

(4) U.S. Patent No. 4,931,450;

(5) U.S. Patent No. 5,071,859;

(6) Pavia, Michael R., et al.: Structure-Activity Studies on Benzhydrol-Containing Nipecotic Acid and Guvacine Derivatives as Potent, Orally-Active Inhibitors of GABA Uptake. In: J. Med. Chem. 1992, 35, pp. 4238-4248;

(7) Andersen, Knud Erik, et al.: The Synthesis of Novel GABA Uptake Inhibitors. 1. Elucidation of the Structure-Activity Studies Leading to the Choice of (R)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic Acid (Tiagabine) as an Anticonvulsant Drug Candidate. In: J. Med. Chem. 1993, 36, pp. 1716-1725;

(8) Suzak, Peter D.: Lipophilic GABA uptake inhibitors: Biochemistry, pharmacology and therapeutic potential. In: Drugs of the Future 1993, 18(12), pp.1129-1136;

(9) Murali Dhar, T.G., et al.: Design, Synthesis and Evaluation of Substituted

Triarylnipecotic Acid Derivatives as GABA Uptake Inhibitors: Identification of a Ligand with Moderate Affinity and Selectivity for the Cloned Human GABA Transporter GAT-3. In: J. Med. Chem. 1994, 37, pp. 2334-2342; and

(10) Thomsen, C., et al.: 1-(3-(9H-Carbazol-9-yl)-1-propyl)-4-(2-methoxyphenyl)-4-piperidinol, a novel subtype selective inhibitor of the mouse type II GABA-transporter. In: British Journal of Pharmacology (1997) 120, 983-985.

Like BONDINELL, SONNEWALD and ALI, all of the above documents relate to 3-substituted compounds (and/or 4-substituted compounds in the case of 6-membered rings) which are reported to show GABA uptake inhibitory action. In contrast thereto, there appear to be no documents which were published before the priority date of the present invention (i.e., before September 5, 1998) and show GABA uptake inhibitors which are structurally of the same type as the compounds of the present invention and comprise a 2-substituted N-heterocyclic ring and, in particular, a 2-substituted pyrrolidine ring. This provides ample evidence of the level of ordinary skill in the pertinent art at the time the present invention was made. In particular, what the totality of the submitted documents strongly suggests is that at the time the present invention was made those of skill in the art of GABA uptake inhibitors had accepted that only compounds having a COOM substituent on a ring carbon atom not adjacent to the ring nitrogen atom (i.e., compounds without a COOM substitutent in 2-position) are useful as GABA uptake inhibitors.

Stated differently, contrary to the Examiner's allegation, the totality of the documents of record provides evidence that those of skill in the art did not have an expectation that 2-substituted compounds would have an activity as GABA uptake inhibitors similar to that of the 3-substituted compounds investigated by them.

e. 2-Substituted Compounds Were Available, But Were Not Investigated As GABA Uptake Inhibitors

There are no apparent reasons other than the lack of expectation of success for the lack of interest in 2-substituted compounds by those of skill in the pertinent art. In particular, synthetic obstacles do not appear to have existed. In fact, 2-substituted compounds have been disclosed, albeit for different applications. In this regard, three further documents submitted with Appellants' Information Disclosure Statement may be referred to, i.e., WO 97/45115 A (a family member of U.S. Patent No. 6,191,165 to Ognyanov et al., i.e., the only document cited in the first Office Action mailed December 26, 2001) and GB 2 145 081 A and its family member, U.S. Patent No. 4,610,995. However, neither of these documents relate to GABA uptake inhibitors. Rather, these documents relate to inhibitors of the glycine transport via the Gly-T-1 or Gly-T-2 transporters and to anti-histamines, respectively.

Accordingly, the totality of the numerous documents of record in the present application, including the documents relied on by the Examiner, shows that the present inventors proceeded contrary to the accepted wisdom in the art by employing 2-substituted compounds for the inhibition of GABA uptake rather than 3-(4-) substituted compounds used

by numerous other researchers in this field.

f. Those Skilled in the Art Had Disregarded 2-Substituted Compounds For More Than a Decade

The Examiner argues "that position isomerism has been used as a tool to obtain new and useful drugs and position isomerism is a fact of close structural similarity". However, the Examiner fails to take into account that in the present case there is clear evidence that those of skill in the art apparently did not consider position isomerism to be a useful tool for obtaining new and useful GABA uptake inhibitors. In this regard, it is to be pointed out that at the time the present invention was made, research in the field of GABA uptake inhibitors of the type claimed in the present invention had been going on for much more than a decade (note that the filing date of, for example, BONDINELL is October 25, 1982, more than 15 years before the priority date of the present invention). This would have given those of skill in the art ample time to investigate 2-substituted analogs of any of the known 3-substituted GABA uptake inhibitors. The fact that those skilled in the art apparently did not consider it worthwhile to study 2-substituted compounds with respect to their property as potential GABA uptake inhibitors for many years (otherwise they most likely would have published the results of their studies) and focused exclusively on structural variations of the known 3-substituted compounds without changing the 3-substitution on the heterocyclic ring is yet another strong indication of non-obviousness of the claimed subject matter. Accordingly, a *prima facie* case of obviousness of claims 31-61 has not been established for this additional

reason.

B. The Rejected Claims Do Not Stand or Fall Together

At least claims 31-56, claims 59 and 60, and claim 61 are patentable for separate reasons. It is noted that in light of the documents relied on in the final rejection, compound claims 41-43, 48, 53 and 55 are separately patentable as well, inasmuch as these documents do not teach or suggest any group Z as defined in these claims. However, it also is noted that corresponding groups Z are shown in documents (8) and (9) referred to in Section VIII.A.d. above in combination with GABA uptake inhibitors having a 3-substituted N-heterocyclic ring.

1. Claims 31-56

Compound claim 31, and claims 32-56 depending therefrom, define compounds of general formula (I) as recited in claim 31, all of which have in common that the pyrrolidine ring structure thereof is 2-substituted by a group of formula $-A^1-X$. As discussed above, none of the documents relied on in the final rejection, i.e., BONDINELL, SONNEWALD and ALI, teaches or suggests a compound having a N-heteroaromatic ring with such a group $-A^1-X$ in the 2-position. Therefore, even if it were concluded that any of the remaining composition and method claims 57-61 are not patentable in view of the references relied on in the final rejection for any reason, this reason would not be sufficient to justify a rejection of compound claims 31-56 as *prima facie* obvious over the cited documents.

2. Claims 59 and 60

Composition claim 59 and claim 60 dependent therefrom are directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of general formula (I) as recited in claim 59, with claim 60 reciting a preferred subgenus of the compounds recited in claim 59. As discussed, none of the documents relied on in the final rejection, i.e., BONDINELL, SONNEWALD and ALI, teaches or suggests a compound of general formula (I) as recited in claims 59 and 60, let alone a pharmaceutical composition comprising such a compound. Therefore, even if it were concluded that any of the remaining compound and method claims 31-58 and 61 are not patentable in view of the references relied on in the final rejection for any reason, this reason would not be sufficient to justify a rejection of composition claims 59 and 60 as *prima facie* obvious over the cited documents.

3. Claim 61

Claim 61 is directed to a method of treating a disease which can be ameliorated or cured by amplification of GABAergenic neurotransmission. According to this method, a compound as recited in independent claim 31 is administered to a patient in need of such treatment in an amount sufficient to ameliorate or cure the disease. As discussed above, none of the documents relied on in the final rejection, i.e., BONDINELL, SONNEWALD and ALI, teaches or suggests a (2-substituted) compound as recited in present claim 31.

Additionally, even if it were assumed, *arguendo*, that such a teaching or suggestion may be found in any of these documents, these documents would still not teach or suggest the use of a corresponding compound for the treatment of a disease which can be ameliorated or cured by amplification of GABAergenic neurotransmission. Therefore, even if it were concluded that any of the remaining compound, composition and method claims 31-60 are not patentable in view of the references relied on in the Final Rejection for any reason, this reason would not be sufficient to justify a rejection of method claim 61 as *prima facie* obvious over the cited documents.

IX. CONCLUSION

For the reasons set forth above, it is respectfull submitted that the Examiner has failed to establish a *prima facie* case of obviousness, which is a prerequisite for maintaining a rejection under 35 U.S.C. § 103. The Board is, therefore, respectfully requested to reverse the Final Rejection, and to allow the application to issue in its present form.

Respectfully submitted,
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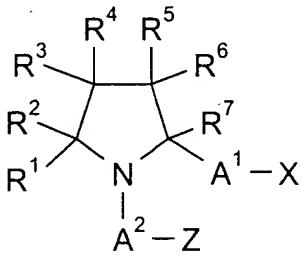
APPENDIX
Copy of Rejected Claims
Rejected Claims 31-61

31. A compound of formula (I)



(I)

wherein

R^1 to R^7 are independently selected from H, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, optionally substituted aryl or heteroaryl, OH, halogen, CN, OR^{12}, SR^{12}, COR^{12}, $COOR^{12}$, SOR^{12}, SO_2R^{12}, $NR^{13}R^{14}$, $CONR^{13}R^{14}$, $SO_2NR^{13}R^{14}$, where R^{13} and R^{14} are independently selected from H and C_{1-3} alkyl and R^{12} represents C_{1-6} alkyl ; two of R^1 to R^7, together with the atoms connecting them, each may form a 3- to 6-membered ring system, which ring system may contain one or more heteroatoms; at least one of the pairs R^1 and R^2; R^3 and R^4; and R^5 and R^6 may be replaced by an optionally substituted alkylidene group or =O; and two of R^1 to R^7 which are positioned at adjacent carbon atoms may each be replaced by a C-C bond;

A^1 is selected from $(-CR^8R^9-)_n$, optionally substituted C_{3-6} cycloalkylene and a combination of these groups, R^8 and R^9 being independently selected from H, C_{1-6} alkyl,

halogen, OH, OR^{12} and $NR^{13}R^{14}$ and where for $n \geq 2$, R^8 and R^9 may be different in each group and two groups selected from R^8 and R^9 at adjacent C atoms may be replaced by a C-C bond, and a group -O- or -CO- may be positioned between two adjacent groups CR^8R^9; and wherein one of R^8 and R^9 may be combined with one of R^1 to R^7 to form a 5- to 7-membered ring structure; and n = 1, 2, 3 or 4;

X is selected from COOM and groups which can be converted into COOM under physiological conditions, M being selected from H and pharmaceutically acceptable cations;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H, C_{1-2} alkyl and halogen; where for $m \geq 2$ the groups R^{10} and R^{11} may be different in each group, a group -O- or -S- may be positioned between two adjacent groups $-CR^{10}R^{11}-$, and two groups selected from R^{10} and R^{11} at adjacent C atoms may be replaced by a C-C bond; and wherein one of R^{10} and R^{11} may be combined with one of R^1 to R^9 to form a 5- to 7-membered ring structure; and m is 1, 2, 3, or 4;

Z is selected from Y_3C-O-, $Y_2C{=}CR^{15}$- and $Y_2C{=}N$-O-, where R^{15} is selected from H, C_{1-3} alkyl or halogen and the groups Y are independently selected from optionally substituted C_{6-12} aryl and optionally substituted C heteroaryl having up to three heteroatoms independently selected from N, O and S, and the groups Y may be linked by a covalent bond or by groups between atoms belonging to different groups Y, said groups selected from -O-, -S-, -NH-, -O-, -CH=CH-, -CH=N-, $-CH_2-$ and $-CH_2CH_2-$;

as well as the individual stereoisomers of these compounds.

32. The compound of claim 31, wherein R^7 is hydrogen and R^1 to R^6 are independently selected from hydrogen, optionally substituted C_{1-3} alkyl, halogen, OH, CN, optionally substituted phenyl and optionally substituted heteroaryl having 5 to 10 ring members and one or two heteroatoms selected from O, N and S.

33. The compound of claim 32, wherein R^1 to R^6 are independently selected from hydrogen, C_{1-3} alkyl and phenyl.

34. The compound of claim 33, wherein all of R^1 to R^7 represent hydrogen.

35. The compound of claim 31, wherein A^1 is $(-CR^8R^9-)_n$, R^8 and R^9 are independently selected from H and C_{1-3} alkyl and n has a value of 1, 2 or 3.

36. The compound of claim 35, wherein R^8 and R^9 are each hydrogen and n has a value of 1 or 2.

37. The compound of claim 34, wherein X is COOM, with M = H, Na, K, NH_4, $Ca_{0.5}$ or $Mg_{0.5}$.

38. The compound of claim 37, wherein X is selected from H and Na.

39. The compound of claim 31, wherein R^{10} and R^{11} are independently selected from H and C_{1-2} alkyl and m is 2 or 3.

40. The compound of claim 39, wherein R^{10} and R^{11} are each H and m = 2.

41. The compound of claim 35, wherein Z is Y_3C-O- and the groups Y are phenyl groups optionally substituted with one to two substituents selected from C_{1-3} alkoxy, C_{1-3} alkyl, halogen, OH, NO_2, CN and $NR^{13}R^{14}$.

42. The compound of claim 41, wherein the groups Y are identical and represent phenyl substituted with one C_{1-3} alkoxy group.

43. The compound of claim 42, wherein the phenyl groups are para-substituted with a C_{1-2} alkoxy group.

44. The compound of claim 31, wherein Z is $Y_2C=CR^{15}$-, the groups Y are selected from optionally substituted phenyl and optionally substituted heteroaryl having 5 to 6 ring members and one to two heteroatoms independently selected from O, N and S and R^{15} is selected from H and CH_3.

45. The compound of claim 44, wherein R^{15} is H.

46. The compound of claim 45, wherein the groups Y carry 0, 1 or 2 substituents, the substituents being selected from C_{1-3} alkyl, C_{1-3} alkoxy, halogen, OH, NO_2, CN and $NR^{13}R^{14}$.

47. The compound of claim 44, wherein the groups Y are the same and are selected from phenyl, 4-methoxyphenyl and 3-methyl-2-thienyl.

48. The compound of claim 31, wherein Z is $Y_2C=N-O-$ and the groups Y are selected from optionally substituted phenyl and optionally substituted heteroaryl having 5 to 6 ring members and one to two heteroatoms independently selected from O, N and S.

49. The compound of claim 31, wherein

R^1 to R^7 are independently selected from H, C_{1-3} alkyl and phenyl;

A^1 represents $(-CR^8R^9-)_n$, R^8 and R^9 are independently selected from H and C_{1-3} alkyl, and n = 1 or 2;

X is selected from COOM and groups which can be converted into COOM under physiological conditions, M being selected from H and Na;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H and C_{1-2} alkyl and m is 2 or 3; and

Z is selected from Y_3C-O- and $Y_2C{=}CR^{15}$-, R^{15} is selected from H and methyl and the groups Y are identical and selected from optionally substituted C_{6-12} aryl and optionally substituted C_{2-5} heteroaryl having up to three heteroatoms independently selected from N, O and S.

50. The compound of claim 49, wherein R^1 to R^7 are independently selected from H and methyl.

51. The compound of claim 50, wherein R^8 and R^9 are independently selected from H and methyl, and n = 1.

52. The compound of claim 49, wherein R^{10} and R^{11} are independently selected

from H and C_{1-2} alkyl and m is 2 .

53. The compound of claim 52, wherein Z is Y_3C-O- and the groups Y are identical and represent phenyl substituted with one C_{1-3} alkoxy group.

54. The compound of claim 49, wherein Z is Y_2C=CH- and the groups Y are identical and selected from phenyl, 4-methoxyphenyl and 3-methyl-2-thienyl.

55. The compound of claim 49, wherein

R^1 to R^7 are each H;

A^1 represents $(-CR^8R^9-)_n$, R^8 and R^9 are independently selected from H and methyl, and n = 1 or 2;

X is COOM and M is selected from H and Na;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H and methyl and m is 2; and

Z is Y_3C-O- and the groups Y are identical and selected from phenyl groups para-substituted with a C_{1-2} alkoxy group.

56. The compound of claim 49, wherein

R^1 to R^7 are each H;

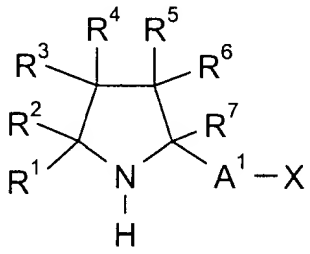
A^1 represents $(-CR^8R^9-)_n$, R^8 and R^9 are independently selected from H and methyl, and n = 1 or 2;

X is COOM and M is selected from H and Na;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H and methyl and m is 2; and

Z is $Y_2C=CH-$ and the groups Y are identical and selected from phenyl, 4-methoxyphenyl and 3-methyl-2-thienyl.

57. A process for the preparation of a compound of formula (I) of claim 31, wherein a compound of formula (II)



(II)

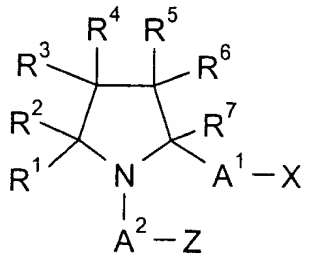
wherein R^1 to R^7, A^1 and X are as defined in claim 31 is reacted with a compound of formula (III):

$$D - A^2 - Z \quad \text{(III)}$$

wherein A^2 and Z are defined as in claim 31 and D represents a group which can react with the group N-H of the compound of formula (II) to form HD.

58. The process of claim 57, wherein D is halogen.

59. A pharmaceutical composition comprising at least one of a pharmaceutically acceptable carrier and a pharmaceutically acceptable excipient and at least one compound of formula (I):



(I)

wherein

R^1 to R^7 are independently selected from H, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, optionally substituted aryl or heteroaryl, OH, halogen, CN, OR^{12}, SR^{12}, COR^{12}, $COOR^{12}$, SOR^{12}, SO_2R^{12}, $NR^{13}R^{14}$, $CONR^{13}R^{14}$, $SO_2NR^{13}R^{14}$, where R^{13} and R^{14} are independently selected from H and C_{1-3} alkyl and R^{12} represents C_{1-6} alkyl ; two of R^1 to R^7, together with the atoms connecting them, each may form a 3- to 6-membered ring system, which ring system may contain one or more heteroatoms; at least one of the pairs R^1 and R^2; R^3 and R^4; and R^5 and R^6 may be replaced by an optionally substituted alkylidene group or

=O; and two of R^1 to R^7 which are positioned at adjacent carbon atoms may each be replaced by a C-C bond;

A^1 is selected from $(-CR^8R^9-)_n$, optionally substituted C_{3-6} cycloalkylene and a combination of these groups, R^8 and R^9 being independently selected from H, C_{1-6} alkyl, halogen, OH, OR^{12} and $NR^{13}R^{14}$ and where for $n \geq 2$, R^8 and R^9 may be different in each group and two groups selected from R^8 and R^9 at adjacent C atoms may be replaced by a C-C bond, and a group -O- or -CO- may be positioned between two adjacent groups CR^8R^9; and wherein one of R^8 and R^9 may be combined with one of R^1 to R^7 to form a 5- to 7-membered ring structure; and n = 1, 2, 3 or 4;

X is selected from COOM and groups which can be converted into COOM under physiological conditions, M being selected from H and pharmaceutically acceptable cations;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H, C_{1-2} alkyl and halogen; where for $m \geq 2$ the groups R^{10} and R^{11} may be different in each group, a group -O- or -S- may be positioned between two adjacent groups $-CR^{10}R^{11}-$, and two groups selected from R^{10} and R^{11} at adjacent C atoms may be replaced by a C-C bond; and wherein one of R^{10} and R^{11} may be combined with one of R^1 to R^9 to form a 5- to 7-membered ring structure; and m is 1, 2, 3, or 4;

Z is selected from Y_3C-O-, $Y_2C{=}CR^{15}$- and $Y_2C{=}N$-O-, where R^{15} is selected from H, C_{1-3} alkyl or halogen and the groups Y are independently selected from optionally substituted

C_{6-12} aryl and optionally substituted C_{2-5} heteroaryl having up to three heteroatoms independently selected from N, O and S, and the groups Y may be linked by a covalent bond or by groups between atoms belonging to different groups Y, said groups selected from -O-, -S-, -NH-, -O-, -CH=CH-, -CH=N-, $-CH_2-$ and $-CH_2CH_2-$.

60. The pharmaceutical composition of claim 59, wherein

R^1 to R^7 are independently selected from H, C_{1-3} alkyl and phenyl;

A^1 represents $(-CR^8R^9-)_n$, R^8 and R^9 are independently selected from H and C_{1-3} alkyl, and n = 1 or 2;

X is selected from COOM and groups which can be converted into COOM under physiological conditions, M being selected from H and Na;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H and C_{1-2} alkyl and m is 2 or 3; and

Z is selected from Y_3C-O- and $Y_2C=CR^{15}$-, R^{15} is selected from H and methyl and the groups Y are identical and selected from optionally substituted C_{6-12} aryl and optionally substituted C_{2-5} heteroaryl having up to three heteroatoms independently selected from N, O and S.

61. A method of treating a disease which can be one of ameliorated and cured by

amplification of GABAergenic neurotransmission, the method comprising administering to a patient in need of such treatment a compound of claim 31 in an amount sufficient to ameliorate or cure the disease.